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Aggressive approach and outcome in patients presenting atrial fibrillation and hypertension

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ABSTRACT

Aim: Aggressive approach in patients presenting atrial fibrillation (AF) and hypertension could result in improving rhythm control and reducing admission.
Methods: Out of 3475 patients presenting AF, those with hypertension (n = 1739, 52%) underwent standard (n = 591, group 1, years 2004–2005) or aggressive pharmacological and electrical approach (n = 1148, group 2, years 2006–2009). Overall, in 1071 patients AF duration was less than 48 h. Primary endpoint was rhythm conversion; secondary endpoints were modalities of rhythm conversion and reduction of admissions.
Results: At univariate and multivariate analyses, AF lasting less than 48 h, absence of comorbidities and younger age were independent predictors of sinus rhythm; conversely, lack of sinus rhythm, older age, AF lasting more than 48 h and comorbidities were independent predictors of hospitalization. Overall, 55% of patients achieved sinus rhythm in group 1 versus 62% in group 2 ($p = 0.018$). Interestingly, in patients with AF lasting less than 48 h, 89% achieved sinus rhythm, more likely by class 1C than by class III antiarrhythmic drugs ($p < 0.001$). Overall reduction of admission accounts for 60%; 50% of patients need admission in group 1 versus 29% in group 2 ($p < 0.001$).
Conclusions: Aggressive pharmacological and electrical approach in patients presenting AF and hypertension significantly improved rhythm conversion overall up to 62%. Patients with AF lasting less than 48 h eventually achieved sinus rhythm up to 89%, mostly by class IC antiarrhythmic drugs. Admissions eventually reduced up to 60%.

1. Introduction

In emergency settings, effective therapeutic management of atrial fibrillation (AF) is not yet clear, because of lack of understanding of several pathophysiological aspects of arrhythmia and because the existing possibility of the underlying presence of structural heart disease to which several pharmacological side effects are related. Moreover, to date there has been no convincing evidence that antiarrhythmic or antihypertensive therapy and 'rhythm control' is better than the rate control approach [1–3]. However, recent data have shown therapeutic success might be associated with rhythm-control and clinical outcomes driven by hospitalizations for arrhythmia and other comorbidities [4]. Atrial fibrillation is established to share strong epidemiological associations with a large panel of risk factors including advanced age, male sex, diabetes mellitus and especially hypertension or with several diseases including heart failure, coronary artery disease, valvular heart disease and thyroid disease [5,6]. Atrial fibrillation could also be the effect of an underlying 'masked' disorder associated with metabolic syndrome and its components, sleep apnea, inflammation, and aspects of lifestyle as alcohol consumption and physical activity. Eventually, in some patients with AF, no underlying pathology is present and the etiology remains unknown [7]. Detection of the underlying disorder may result in implementation of effective treatment that could improve outcomes, but the presence of structural heart disease as in patients with hypertension should not to be considered as absolute contraindication to aggressive approach and rhythm control. The aim of the present study was to evaluate if aggressive approach in patients with AF and hypertension without moderate to severe structural heart disease could result in improving rhythm control and eventually reducing admission in a large series of patients presenting to the Emergency Department [8].

2. Materials and methods

The study enrolled AF patients presenting to the Emergency Department of the tertiary care teaching hospital, in Florence, Italy. Facilities for triage of patients with suspected dysrhythmia included an Observation Unit with 6 monitor equipped beds

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and dedicated personnel (resident, faculty, and cardiologist on call). Coded diagnoses are entered into an electronic medical chart, allowing easy selection of all patients with a diagnosis of interest. Data were collected from January 2004 to December 2010.

2.1. Patient selection

Inclusion criteria were the presence of AF documented by ECG. Consecutive patients presenting to the Emergency Department complaining of palpitations or malaise were considered and those with AF documented by ECG were evaluated and enrolled in the study. Exclusion criteria were age<18 years, Killip Class ≥2, New York Heart Association functional class≥III, clinically detectable ongoing complications like acute coronary syndrome, stroke and pulmonary or peripheral embolism, and hemodynamic instability. Patients with moderate to severe structural heart disease were excluded from the study. All patients gave their consent for study participation. The study was conducted according to good clinical practice and the Helsinki Principles.

2.2. Definition of subtype of AF, structural heart disease and comorbidities

Paroxysmal AF was defined by electrocardiographic evidence of AF followed by subsequent ECG showing sinus rhythm or clinical documentation by a physician of paroxysmal AF; persistent AF was defined when lasting longer than 7 days or when terminated by therapeutic treatment; permanent AF (or chronic AF) was defined in the presence of serial electrocardiograms showing only AF and no interim evidence of sinus rhythm; solitary AF was defined by AF in the absence of overt cardiovascular disease or precipitating illness [9]. Systemic hypertension was defined by need for antihypertensive therapy or the presence of systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Coronary artery disease was defined by angiographic findings of stenosis >50% in any of the 3 main arterial distributions, effort angina, or history of myocardial infarction. Moderate to severe valvular heart disease was considered in the presence of substantial murmur on physical heart examination, or by history of documented prior valve repair/replacement or by echocardiography confirmation. Congestive heart failure was defined by a physician's diagnosis or by need for treatment with dedicated drug treatment. Carotid artery disease referred to the presence of stenosis>50% in the carotid arteries based on neurovascular imaging or previous intervention. Stroke included development of any type of stroke, as defined by clinical documentation of the diagnosis with or without confirmatory findings on imaging studies. Diabetes mellitus was defined by a physician's diagnosis or by need for treatment with insulin or oral hypoglycemic agents. Chronic obstructive pulmonary disease and dysthyroidism were defined by a physician's diagnosis as documented in the medical records. Abnormal kidney function was defined as the presence of equivalent serum creatinine ≥200 mmol/L or renal transplant or the presence of chronic dialysis. 'Abnormal liver function' was defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin>2× upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3× upper limit normal, etc.). Also patients with other chronic diseases (e.g. immunity disorders and cancer) and eventually at short-term life expectancy were considered.

2.3. Management of patients and study protocol

All patients underwent evaluation with medical history, physical examination, blood tests, serial ECGs and plasma levels of Troponin I. Chest radiograph, blood gas analysis and echocardiogram were performed according to the clinical conditions. Patients with AF onset less than 48 h and without moderate to severe structural heart disease were considered eligible for rhythm control and received within the first-line 6-hour period i.v. bolus (in a few minutes) Flecainide (2 mg/kg), Propafenone (2 mg/kg), or Amiodarone (5 mg/kg), [9–13]. Patients who did not recover sinus rhythm could be submitted to a second dose of drugs previously given, eventually followed by oral administration up to 24 h of Flecainide (2 mg/kg plus 100 mg twice a day), Propafenone (2 mg/kg plus 150 mg three times a day), or Amiodarone (5 mg/kg plus 200 mg twice a day). After the first or second-line approach, patients could be submitted to early or elective electrical conversion (previous transesophageal echocardiography or after 3 weeks anticoagulation, respectively). After DC shock, patients were observed for a period of 6 h to promptly detect adverse events. No randomization was used and the therapeutic approach was at the discretion of the physician on duty [9].

2.4. Patients considered for enrollment in the study

Two groups of patients were considered. Group 1 included those patients presenting to the Emergency Department between January 2004 and December 2005 managed with standard approach; conversely group 2 included those patients presenting between January 2006 and December 2009 managed with aggressive treatment strategy in the Intensive Observation Unit and eventually additional Outpatient Clinic. Treatment strategy included intensive pharmacological treatment followed by electrical treatment as required. Hypertension, diabetes mellitus, comorbidities, AF duration (less or more than 48 h), quality of therapeutic approach and rhythm conversion or lack of rhythm control were analyzed.

2.4.1. Endpoint

Primary endpoint included rhythm conversion; secondary endopoints included modalities of rhythm conversion and reduction of admissions.

2.5. Statistical analysis

Summary data are expressed as mean ± SD. Statistical comparisons of demographic and clinical features among the 2 groups were performed using $\chi 2$ test for non parametric variables, as required. Analysis of variance was used for parametric variables. Univariate and multivariate logistic regression were used to define independent predictors of hospitalization. *P* values are 2 sided. A *p* value <0.05 was considered statistically significant. Calculations were performed with version 17, SPSS statistical package (SPSS Inc, Chicago, IL).

3. Results

From January 2004 to December 2009, 3475 AF patients presenting to the Emergency Department (1.1% of total visits per year) were considered for enrolment in the study. Those with hypertension (1739, 52%) and without moderate to severe structural heart disease were enrolled and stratified into two groups: group 1 (years 2004–2005) included 591 patients and group 2 (years 2006–2009) included 1148 patients. Baseline clinical characteristics of enrolled patients are shown in Table 1. In our series approximately two-third of patients presented AF lasting less than 48 h; one-half showed male gender and one-half comorbidities; mean age was 72 years. Due to the prospective observational design of the study, differences existed among clinical characteristics of the two groups of patients including male gender, comorbidities and duration of AF. Mean age was the same (Table 1). At univariate and multivariate analyses, AF lasting less than 48 h, absence of comorbidities and younger age were independent predictors of sinus rhythm (Table 2). Conversely, lack of sinus rhythm, older age, AF lasting more than 48 h, presence of comorbidities and diabetes were independent predictors of hospitalization (Table 3).

Overall, 1039 (60%) patients achieved sinus rhythm; we found a strong association between lower decades of age and conversion to sinus rhythm in patients with atrial fibrillation and hypertension enrolled in the study (Fig. 1). However, 55% patients achieved sinus rhythm in group 1 versus 62% in group 2 ($p=0.018$, Table 4). Spontaneous, electrical or pharmacological conversion account for 24%, 8% and 68% in group 1 versus 30%, 21% and 49% in group 2 ($p<0.001$, Table 4). Interestingly, out of 1071 patients with AF lasting less than 48 h, 950 (89%) achieved sinus rhythm as follows: 249 (26%) spontaneously, 160 (17%) by electrical conversion and 541 (57%) by intensive pharmacological approach (394 with class 1C and 147 with class III antiarrhythmic drugs, 73% and 27%, respectively, $p<0.001$, Fig. 3). In this subset of patients, spontaneous, electrical or pharmacological conversion account for 23%, 7% and 70% in group 1 versus 28%, 21% and 51% in group 2 ($p<0.001$). In both groups, patients more likely achieved sinus rhythm by class 1C as compared to class III antiarrhythmic drugs ($p<0.001$, Table 5). Overall, only 36% (n=629) patients need admission; 50% in group 1 versus 29% in group 2; thus reduction of admission accounts for up to 60% ($p<0.001$, Fig. 2). In our series, we found a strong association between higher decades of age and admission to hospital (Fig. 4).

Table 1
Baseline clinical characteristics of patients with atrial fibrillation and hypertension enrolled in the study (n=1739).

Clinical characteristics	Total (n=1739)	Group 1 (n=591)	*p*	Group 2 (n=1148)
Age (years s.d.)	72 11	72 ± 11	0.478	73 ± 11
Gender (male)	793 (46%)	247 (42%)	0.022	546 (48%)
Diabetes mellitus	202 (12%)	57 (10%)	0.069	145 (13%)
Comorbidities	747 (43%)	277 (47%)	0.019	470 (41%)
AF<48 h	1071 (62%)	320 (54%)	<0.001	751 (65%)
Sinus rhythm	1039 (60%)	330 (56%)	0.018	709 (62%)
Discharge	1110 (64%)	296 (50%)	<0.001	814 (71%)

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Table 2
Association between clinical variables and sinus rhythm at univariate and multivariate analyses.

	Univariate analysis			Multivariate analysis		
	OR	Confidence interval 95%	p	OR	Confidence interval 95%	p
AF lasting <48 h	51.077	38,132–68,436	<0.001	47.890	35,626–64,377	<0.001
Comorbidities	1.911	1.573–2.322	<0.001	1.687	1.247–2.264	<0.001
Age	0.961	0.951–0.970	<0.001	0.962	0.969–0.996	<0.001
Diabetes mellitus	1.834	0.1366–2.463	<0.001	–	–	–
Male gender	0.960	0.792–1.164	0.680	–	–	–

4. Discussion

Detection of the underlying AF disorder even clinically 'masked' could result in implementing effective treatment and improving prognosis [6,8,14]. Suggestion resulted in reducing aggressive approach to AF patients. Indeed in the past decades clinical pathways pursued conversion to sinus rhythm, in patients presenting AF, when no structural heart disease was detected. At the same time this condition was considered to be associated essentially with isolated AF which accounted for almost 30% of all AF cases [1,6,15]. However, recent studies have demonstrated that lone AF is quite a rare disorder. Scientists from the Mayo Clinic of Olmsted County in the American state of Minnesota examined, between 1950 and 1980, 3623 patients with a first episode of AF and followed up them until 2003. Data revealed that only 2% of the total population of patients with AF really presented isolated AF with no concomitant heart disease, diabetes mellitus, hypertension or noncardiac disease that potentially could shorten life expectancy [7]. In the Framingham Heart Study, hypertension and diabetes were the sole cardiovascular risk factors to be predictive of AF after controlling for age and other predisposing conditions [16]. Thus, the role of hypertension as risk factor for AF is established; however, despite its leading importance as a highly prevalent and modifiable risk factor, only a few data are available regarding predictors and outcome of AF in hypertension. Extrapolations of results to uncomplicated hypertensive subjects with possible coexistence of LV hypertrophy could lead to improve aggressive treatment to pursue sinus rhythm [5,6,17].

The present study shows approximately two-third of patients presenting AF and hypertension achieved sinus rhythm when submitted to aggressive approach versus standard approach ($p = 0.018$, Table 2). In addition, four-fifth of patients with AF lasting less than 48 h achieved sinus rhythm without difference between groups; patients more likely achieved sinus rhythm by class 1C than by class III antiarrhythmic drugs ($p < 0.001$, Table 5). Strong independent predictors of sinus rhythm were AF lasting less than 48 h, absence of comorbidities (Table 2) and younger age (Fig. 1). Overall reduction of admission with aggressive versus standard approach accounts for 60%, 50% versus 29%, respectively ($p < 0.001$, Fig. 2). Independent predictors of hospitalization were lack of sinus rhythm, AF lasting more than 48 h, presence of comorbidities (Table 3) and older age (Fig. 4). Consistent with our findings, previous studies have reported that hypertension accounts for more than one-half in patients presenting AF, and aggressive approach could result in improving sinus rhythm and reducing admission. In fact, in the Manitoba Follow-up study, prevalence of hypertension was 53%, and the risk of AF in hypertensive subjects was increased by 1.4 times, while increased by 1.9 times in the Framingham Heart Study [18]. Because of its high prevalence in the population, hypertension independently accounts for more AF cases than any other risk factor [18,19]. Several other studies stated Observation Units as a rational choice for improving the utilization of health care resources [20], especially for successful treatment of chest pain [21], asthma [22], syncope [23] and eventually for treatment of AF, in order to reduce in-hospital stay [24]. Nonetheless no strategy to pursue normal sinus rhythm including antiarrhythmic drug therapy, conversion and ablation has definitely being shown to reduce the risk of stroke and hospitalization [25], in our setting physicians were strongly invited to consider pharmacological conversion as first line treatment [9]. Hence, among patients who recovered sinus rhythm, pharmacological approach was the most representative therapeutic strategy (55%). However, in our study we observed greater percentage of successful electrical treatment through the 6-year period (8% in group 1 versus 21% in group 2; $p < 0.001$). This fact related with electrical approach as rescue treatment when pharmacological treatment failed. Recently, an observational survey of management of AF in real life has shown therapeutic success was likely associated with rhythm-control. In this large survey enrolling 5171 patients therapeutic success was 54% overall (rhythm control 60% versus rate control 47%) a result driven by control of AF. Duration of AF, older age and heart failure predicted permanent AF

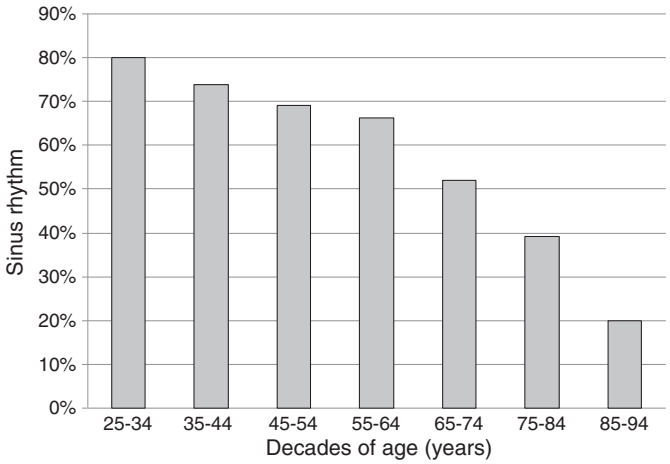

Fig. 1. Association between decades of age and sinus rhythm in patients with atrial fibrillation and hypertension enrolled in the study (n = 1739).

Table 3
Association between clinical variables and hospital admission at univariate and multivariate analyses.

	Univariate analysis			Multivariate analysis		
	OR	Confidence interval 95%	p	OR	Confidence interval 95%	p
Sinus rhythm	8.993	7.186–11.253	<0.001	6.047	4.382–8.445	<0.001
Age	1.040	1.030–1.051	<0.001	1.022	1.010–1.033	<0.001
AF lasting <48 h	0.170	0.137–0.210	<0.001	0.694	0.502–0.960	<0.001
Comorbidities	0.435	0.356–0.531	<0.001	0.544	0.432–0.684	<0.001
Diabetes mellitus	0.489	0.364–0.657	<0.001	0.616	0.437–0.868	0.006
Male gender	1.093	0.898–1.330	0.376	–	–	–

Table 4
Modalities of rhythm conversion in patients enrolled in the study. Class AAD, Vaughan–Williams Class of Anti Arrhythmic Drugs.

	Total n = 1739	Group 1 n = 591	p	Group 2 n = 1148
Sinus rhythm (n, %)	1039 (60%)	330 (56%)	0.018	709 (62%)
Spontaneous conversion (n, %)	289 (28%)	77 (24%)	0.028	212 (30%)
Electrical conversion (n, %)	175 (17%)	27 (8%)	<0.001	148 (21%)
Pharmacological conversion (n, %)	574 (55%)	225 (68%)	<0.001	349 (49%)
Class IC AAD (n, %)	412 (72%)	135 (60%)		277 (79%)
Class III AAD (n, %)	162 (28%)	90 (40%)		72 (21%)

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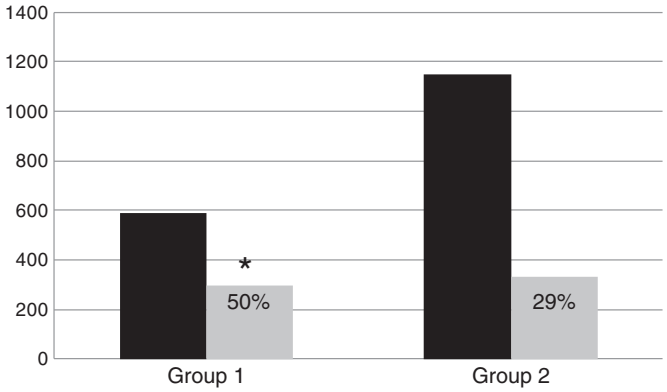

Fig. 2. Patients enrolled in group 1 and 2 (black bars); patients admitted (gray bars). *p<0.001.

[4]. Prevalence of AF and hospitalizations for AF increased in recent years [26,27]; indeed, a report of the American Heart Association showed hospitalizations, with AF as the first-listed diagnosis, increased by 34% from 1996 to 2001 [25]. This trend appears related to the changing practice pattern with AF management [28] rather than changes over time in the distribution of age, sex, and comorbidities [27,29]. As a consequence, AF is a costly public health problem, with hospitalizations as the primary cost driver [30] especially in western countries [31,32]. To date, avoiding hospital admissions becomes mandatory. In our series, aggressive approach to rhythm conversion was planned to reduce admission to hospital. Primary part of the plan considered adherence to guidelines and appropriateness in administration of antiarrhythmic drugs (Fig. 2). Previous trials demonstrated antiarrhythmic drugs succeeded in reducing admissions [13,33] also in patients with structural heart disease [34]. In addition, electrical treatment was considered as rescue treatment after failure of pharmacological approach. Finally, in present study, a substantial portion of patients of group 2 with comorbidities or lack of rhythm control, in whom admission might be considered a real option, was evaluated in Outpatient Clinic for optimization of rate control or rhythm control in order to reduce frequency and severity of AF symptoms, avoiding current admission.

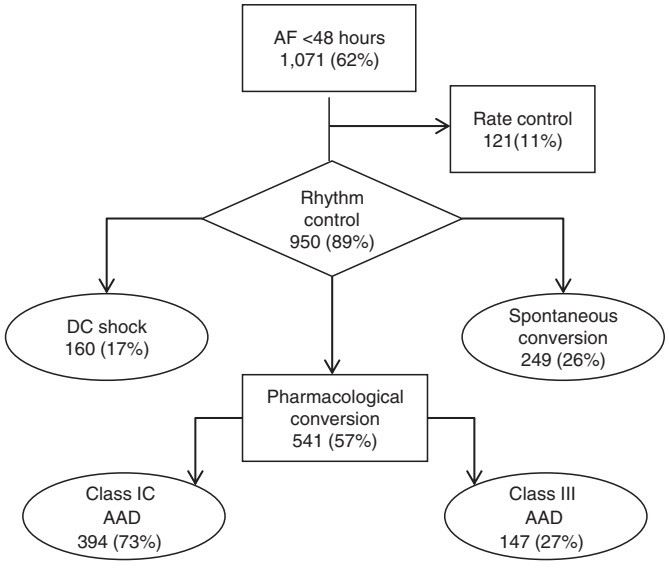

Fig. 3. Diagram of management in patients presenting with atrial fibrillation lasting less than 48 h enrolled in the study. Class ADD, Vaughan–Williams Class of Anti-Arrhythmic Drugs.

Table 5
Modalities of rhythm conversion in patients with atrial fibrillation lasting less than 48 h enrolled in the study. Class AAD, Vaughan–Williams Class of Anti-Arrhythmic Drugs.

	Total n = 1071	Group 1 n = 320	*p*	Group 2 n = 751
Sinus rhythm (n, %)	950 (89%)	280 (88%)	0.460	670 (89%)
Spontaneous conversion (n, %)	249 (26%)	64 (23%)	0.129	185 (28%)
Electrical conversion (n, %)	160 (17%)	20 (7%)	<0.001	140 (21%)
Pharmacological conversion (n, %)	541 (57%)	196 (70%)	<0.001	345 (51%)
Class IC AAD (n, %)	394 (73%)	120 (61%)		274 (79%)
Class III AAD (n, %)	147 (27%)	76 (39%)		71 (21%)

Consistent with this strategy a recent large in-hospital observational registry of AF patients showed that hospitalizations within 2 years after AF diagnosis were associated with increased AF symptom burden and with known limitations of contemporary drug therapy. In this analysis concerning a real world population, the authors suggested that interventions to reduce hospitalization should improve quality of life by reducing symptom frequency and severity rather than just preventing AF recurrences [35]. Although criteria for submission to the Outpatient Clinic were not standardized and at discretion of the emergency physician on duty, we consider this option a remarkable step to avoid current and further hospital admissions.

5. Conclusion

Aggressive pharmacological and electrical approach in patients presenting AF and hypertension significantly improved rhythm conversion overall up to two-third. In those patients presenting AF lasting less than 48 h sinus rhythm accounts for four-fifth. Large part of patients achieved sinus rhythm by pharmacological treatment strategy, mostly by class IC antiarrhythmic drugs. Admissions eventually reduced up to 60%.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [36].

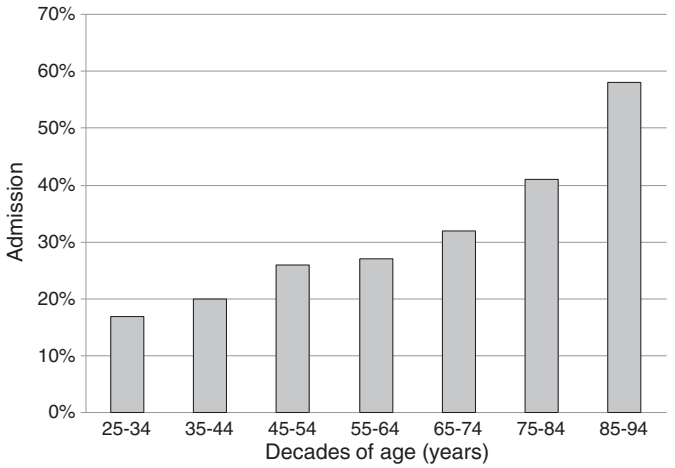

Fig. 4. Association between decades of age and admission to hospital in patients with atrial fibrillation and hypertension enrolled in the study (n = 1739).

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